Metabolic gatekeeper function of B-lymphoid transcription factors.

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Authors: Lai N Chan, Zhengshan Chen, Daniel Braas, Jae-Woong Lee, Gang Xiao, Huimin Geng, Kadriye Nehir Cosgun, Christian Hurtz, Seyedmehdi Shojaee, Valeria Cazzaniga, Hilde Schjerven, Thomas Ernst, Andreas Hochhaus, Steven M Kornblau, Marina Konopleva, Miles A Pufall, Giovanni Cazzaniga, Grace J Liu, Thomas A Milne, H Phillip Koeffler, Theodora S Ross, Isidro Sanchez-Garcia, Arndt Borkhardt, Keith R Yamamoto, Ross A Dickins, Thomas G Graeber, Markus Muschen

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Public Summary:
B-lymphoid transcription factors, such as PAX5 and IKZF1, are critical for early B-cell development, yet lesions of the genes encoding these transcription factors occur in over 80% of cases of pre-B-cell acute lymphoblastic leukaemia (ALL). The importance of these lesions in ALL has, until now, remained unclear. Here, by combining studies using chromatin immunoprecipitation with sequencing and RNA sequencing, we identify a novel B-lymphoid program for transcriptional repression of glucose and energy supply. Our metabolic analyses revealed that PAX5 and IKZF1 enforce a state of chronic energy deprivation, resulting in constitutive activation of the energy-stress sensor AMPK. Dominant-negative mutants of PAX5 and IKZF1, however, relieved this glucose and energy restriction. In a transgenic pre-B ALL mouse model, the heterozygous deletion of Pax5 increased glucose uptake and ATP levels by more than 25-fold. Reconstitution of PAX5 and IKZF1 in samples from patients with pre-B ALL restored a non-permissive state and induced energy crisis and cell death. A CRISPR/Cas9-based screen of PAX5 and IKZF1 transcriptional targets identified the products of NR3C1 (encoding the glucocorticoid receptor), TXNIP (encoding a glucose-feedback sensor) and CNR2 (encoding a cannabinoid receptor) as central effectors of B-lymphoid restriction of glucose and energy supply. Notably, transport-independent lipophilic methyl-conjugates of pyruvate and tricarboxylic acid cycle metabolites bypassed the gatekeeper function of PAX5 and IKZF1 and readily enabled leukaemic transformation. Conversely, pharmacological TXNIP and CNR2 agonists and a small-molecule AMPK inhibitor strongly synergized with glucocorticoids, identifying TXNIP, CNR2 and AMPK as potential therapeutic targets. Furthermore, our results provide a mechanistic explanation for the empirical finding that glucocorticoids are effective in the treatment of B-lymphoid but not myeloid malignancies. Thus, B-lymphoid transcription factors function as metabolic gatekeepers by limiting the amount of cellular ATP to levels that are insufficient for malignant transformation.

Scientific Abstract:
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